Hematological Findings in Medical Professionals Involved at Intraoperative Fluoroscopy

Mohsen Shafiee¹, Elham Hoseinnezhad¹, Hassan Vafapour², Sajad Borzoueisileh¹, Mohammad Ghorbani³ & Razieh Rashidfar¹

Correspondence: Mohsen Shafiee, Cellular and Molecular Research Center, Yasuj University of Medical Sciences, Yasuj, Iran. Tel: 98-91-3139-8984. E-mail: Mohsen.shafiee65@gmail.com

Received: March 16, 2016 Accepted: April 15, 2016 Online Published: April 29, 2016 doi:10.5539/gjhs.v8n12p232 URL: http://dx.doi.org/10.5539/gjhs.v8n12p232

Abstract

Medical professionals involved at intraoperative fluoroscopy are exposed to low doses of the occupational radiation exposures. The biological effects of chronic low-dose radiation on human health are complex and have not been well established. The aim of the present study is to follow up hematological parameter changes during 2 years in medical professionals exposed to ionization radiation in operating rooms.

22 medical professionals (medical specialists and technicians), chronically exposed to ionizing radiation of mobile C-Arm X ray machine, were selected. The seven hematological parameters were examined each time. The statistical analyses were done by Student's t test and one way ONOVA test.

The data analysis led to the following observations: (1) the present study incorporated that the basic hematological parameters including the mean value of red blood cells (P=0.90), white blood cells (P=0.68), and platelets count (P=0.45) did not show a significant difference between two years. (2) The mean values corpuscular hemoglobin concentration, corpuscular hemoglobin, and hematocrit parameters were found disturbed low or high in some of medical professionals but their means were not significantly different between two measurements. (3)A statistically significant relation in mean value of RBCs with the duration of exposure and sex were observed.

It seems that, hematological parameters survey could not be a reliable test as the biological indicator of long term exposure to very low dose of radiation exposure in medical professionals which their physical dosimetry values are lower than dose limits.

Keywords: hematological parameters, medical professionals, intraoperative fluoroscopy, low dose radiation

1. Introduction

Medical specialists and technicians in the intraoperative fluoroscopy are exposed to long-term of low-level radiation during surgical procedures (orthopedic, neurosurgery, urology). These exposures to the surgical team typically come from primary or scatter radiation. The exposure rate for radiation scatter from a mobile C-Arm machine at 2 foot distance from the radiation field is approximately 5millirem/min at 2. Some studies indicated that primary radiation received by medical professionals (MPs) during mobile C-Arm fluoroscopy maybe higher than predicted (Singer, 2005). Often, it is essential that they remain close to the radiation field and therefore cannot use distance to reduce radiation exposure. Numerous studies (Clerinx, Buls, Bosmans, & De Mey, 2008; Klein et al., 2010; Shortt, Al-Hashimi, Malone, & Lee, 2007; Whitby & Martin, 2014) revealed that the occupational radiation doses to the medical specialists and other technicians working with the fluoroscopy are rising health concern.

Over the last several years, there was a trend to investigate the biological effects of the radiation using hematological, biochemical, and cytogenetic parameters (Ossetrova, Sandgren, Gallego, & Blakely, 2010). These investigations have demonstrated that stochastic effects may appear after the exposure to low level radiation

¹ Cellular and Molecular Research Center, Yasuj University of Medical Sciences, Yasuj, Iran

² Medical Physics Department, International Campus, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

³ Department of Basic Sciences, Gonabad University of Medical Sciences, Gonabad, Iran

(Elgazzar & Kazem, 2015). Deterministic effects are well-known and often need higher radiation doses than received by MPs. (Yang et al., 1995) Therefore the concern and unawareness of MPs are related to the stochastic effects of long-term exposure to low-dose radiation. The risk of stochastic effects such as cancer increase by dose without threshold (Muirhead et al., 2009; Venneri et al., 2009). Long-term exposure to low doses of ionizing radiation can affect proliferating cells (Fliedner, Graessle, Meineke, & Feinendegen, 2012) and tissues.

Currently monitoring of long-term exposure of low doses ionizing radiation consists of regular physical dosimetry and also periodic hematological examinations. Some investigations have shown that individual dosimeter might considerably underestimate the real effective dose because theirs reading does not account the radiation exposure of unshielded parts of the body (Siiskonen, Tapiovaara, Kosunen, Lehtinen, & Vartiainen, 2014; von Boetticher, Lachmund, & Hoffmann, 2008). The cells and tissues greatly differ in radiosensitivity. It is important to know that even very low doses radiation may cause radiobiological effects in tissues. Therefore, follow-up of certain specific radiobiological effects provides additional information which complements physical dosimetry and assist better evaluation of radiation effects.

Some of the hematopoietic cells which are very radiosensitive may indicate radiobiological effects of long-term radiation exposure (Smirnova, 2010). Actually, the blood cells count is commonly used as a biodosimeter for occupational exposure (Vorobiev, 1997). The aim of this study was to assess the hematological parameters changes during two years, in medical specialists and technicians, who are being exposed to long-term radiation from intraoperative fluoroscopy.

2. Materials and Methods

2.1 Selection of the Participants

The study was carried out on 3 medical specialists (including Neurologist, Orthopedic surgeon, and Urologist) and 19 technicians (including nurses, anesthesia and operating room staffs) who were chronically exposed to radiation of mobile C-Arm machine in operating rooms of Shahid Beheshti Hospital of Yasuj. 10 men and 12 women were included in this study. The population were divided in three groups, <30, 31-40 and >41, based on their distributions. This hospital performed about more 160 intra-operative fluoroscopies in surgical procedures (orthopedic, neurosurgery, and urology) per month at the time of this study. A questionnaire including demographic characteristics, medical history such as cancer, as well as chronic diseases, history of smoking (subjects who smoked up to 10 cigarettes per day were accepted as smokers) and alcohol consumption were filled by interview for all of the individuals. Each individual who were participated signed an informed consent.

2.2 Exclusion Criteria

Subjects with gross anemia, known history of diabetes mellitus, cardiopulmonary disease, acute or chronic infection, autoimmune disease and malignancy, subjects with current or previous history of smoking or alcohol consumption were excluded from the study. MPs which solely were exposed to low dose of ionizing radiation in the fluoroscopic procedures at the operating rooms of Shahid Beheshti Hospital of Yasuj were included in the study.

2.3 Hematological Methods

Blood samples of all individuals were collected (2ml of blood from each subject) by venipuncture in a disposable syringe and blood was transferred to a tube containing ethylene diamine tetra acetic acid (EDTA) in a concentration of 1.5mg/ml. Hematological parameters (HPs) were measured by an electronic cell counter (Sysmex coulter counter, USA) at laboratory of Yasuj Shahid Beheshti Hospital. Seven HPs were considered for this study including white blood cells (WBC), red blood cells (RBC), and platelet count (PLT), hematocrit (HCT), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular hemoglobin (MCH) and hemoglobin (Hb) which were measured in all subjects. These parameters were compared from 2014 to 2016 years.

2.4 Occupational History

Occupational radiation histories were determined by film badge dosimeter recordings for each MPs which were measured bimonthly by Parsian Radiation Dosimetry Services Company as directed by the Atomic Energy Organisation of Iran. The data were available in their personal records at Shahid Beheshti Hospital. The MPs were protected against radiation by using mobile lead barriers. Also several types of personal shield were used by the medical professionals in this study.

2.5 Statically Analysis

The means of quantitative variables were compared with the independent sample t-test and one-way ANOVA in software SPSS-21. The p values lower than 0.05 assumed as significant.

3. Results

The focus of this study was on the medical professionals' HPs through cell blood count (CBC) test. The participants were being long-term exposed to ionizing radiation of mobile C-Arm x-ray machine and their mean age was 36.84 ± 6.09 years. The film badge records for all of the MPs were under 0.05 milisivert bimonthly from 2014 to 2016. The mean values of examined parameters from 2014 to 2016 are presented in Table 1. We observed that collective mean values of HPs are within the normal range for MPs. Table 1 shows the mean values of WBCs and RBCs count aren't significantly difference between two years with p=0.90 and p=0.68, respectively.

Table 1. Hematological findings from medical professionals during 2014-2016

HPs	High	low	Mean ± SD	Mean ± SD	Normal	n valua
			(2014)	(2016)	range	p-value
WBCs(10 ³ /Cmm)	-	-	6.72 ± 1.02	6.76 ± 1.30	4-10	0.90
RBCs(10 ⁶ /Cmm)	-	3	$4.69 \pm .49$	$4.62 \pm .58$	4-6	0.68
PLT(10³/Cmm)	-	5	205.57±56.67	194.26±43.38	140-400	0.45
Hb(g/L)	5	7	13.64 ± 1.54	13.99 ± 1.60	12-16	0.47
HCT(%)	2	12	38.74 ± 4	40.97 ± 4.27	36-46	0.08
MCH(pg)	5	3	29.14 ± 1.93	30.40 ± 2.46	26-32	0.06
MCHC(g/dl)	16	3	35.46 ± 2.33	34.32 ± 1.67	32-36	0.06

Hb: Hemoglobin, WBCs: White Blood Cells, PLT: Platelet Count, HCT: Hematocrit, RBCs: Red Blood Cells, MCH: Mean Corpuscular Hemoglobin, MCHC: MCH Concentration

Our result indicated that the WBC counts are within the normal range for all individuals .The PLT and RBC counts for 5 and 3 individuals were lower than normal range, respectively. The MCH, MCHC, and HCT parameters were found in the higher and lower normal range for some of the MPs, occasionally. But the Hb parameter was found in the lower and higher range for 5 and 7 individuals, respectively. One way ONOVA test demonstrated that, there is no significant difference in the mean value of HPs with age groups.

Tables 2 and 3 show the means values comparison of RBCs, WBCs and platelet count in MPs on the basis of difference in duration of the ionizing radiation exposure and sex in MPs.

Table 2. Association between mean value of blood cells and duration of exposure in medical professionals

HPs	Duration of exposure	(Mean ± SD)	p-value
	<10	6.88 ± 1.37	
WBCs	11-15	6.79 ± 1.28	0.84
	>16	6.59 ± 1.17	
	<10	$4.21 \pm .42$	
RBCs	11-15	$4.71 \pm .49$	0.02
	>16	$4.82 \pm .54$	
	<10	209.12±38.23	
PLT	11-15	202.40±48.20	0.65
	>16	189.92±59.36	

RBCs: Red Blood Cells, WBCs: White Blood Cells, PLT: Platelet Count, HPs: Hematological Parameters

Table 3. Association	between mean val	lue of blood cell	s and sex in	medical p	professionals

HPs	Sex	(Mean ± SD)	p-value	
WDC	F	6.97 ± 1.27	0.23	
WBCs	M	6.52 ± 1.19	0.23	
DDC	F	$4.26 \pm .42$	0.00	
RBCs	M	$5.05 \pm .28$	0.00	
PLT	F	208.68±46.49	0.22	
	M	190.63±52.58	0.23	

RBCs: Red Blood Cells, WBCs: White Blood Cells, PLT: Platelet Count, F: Female, M: Male, HPs: Hematological Parameters

There were no significant difference between the mean values of WBCs and PLT in all duration of ionizing radiation exposure and gender of MPs The mean values of RBCs in women is significantly lower than men (p<0.001) and the RBC was decreased with duration of exposure (p=0.02). Although, the PLT count was lower for MPs which duration of ionizing radiation exposure were greater than 10 years, its decline did not obtain the significant level (p=0.65).

4. Discussion

Long-term exposure of MPs to low dose radiation has been observed by examining its effect on hematopoietic system. The effect of radiation on hematopoietic and immune system (Hrycek, Czernecka-Micińska, Kłuciński, & Badowski, 2002; Radiation, 2012) suggest that, long-term effects can disturb immunity of medical professionals by suppressing or stimulating the immune system and may induce various hematological diseases (Andreassi et al., 2005; Roguin, Goldstein, & Bar, 2012; Venneri et al., 2009). As shown by Table 1, our results demonstrated that most of the hematological parameters remained within the normal range. Variations in HCT, MCHC and MCH parameters have been noted. Maybe the variation of HCT, MCHC and MCH parameters is related to hemolysis of RBCs as a result of radiations (Yousuf, Mobin, & Leong, 2015) or RBCs deformability.

Table 2 shows, a statistically significant relation between the mean RBCs value with sex, which may be as a result of the fact that, the RBCs count is higher in men than women and maybe it is not as the result of irradiation. Also the relation between the duration of exposure and RBCs count were significant which may be as a result of the age as a confounding factor.

Although, the PLT count was lower in MPs with duration of exposure>10 years, but it was not statically significant. Decline in PLT count with duration of exposure>10 years was confirmed by Rozgaj et al (Rozgaj, Kašuba, Šentija, & Prlić, 1999). PLT play an essential role in blood clotting and wound healing, and they are a strong source of cytokines and growth factors (Semple, Italiano, & Freedman, 2011). Therefore, it is possible that reduction in PLT count of MPs with duration of exposure>10 years could affect these biological procedures (Billings, Romero-Weaver, & Kennedy, 2014). The results about mean value RBCs and WBCs are approved by Meo et all (Meo, 2004) and are conflicting with the other recent studies (Caciari et al., 2011).

The radiobiological effect of hemopoietic system has been shown that it depends on both total absorbed dose, and the dose-rate or frequency of repetitive exposures (Fliedner et al., 2012). Limited data are available about effects of varying in dose-rates and accumulated dose (Fritz, 2002). Sanzari et all suggests that a significant decline in blood cell counts after ionizing radiation depends on dose (Sanzari, Cengel, Wan, Rusek, & Kennedy, 2014) which is similar to findings in some studies that examined animals model after whole-body irradiation (El-Shanshoury, El-Shanshoury, & Abaza, 2016; Sanzari et al., 2013) or have been observed in human (Fliedner et al., 2012; Rozgaj et al., 1999). But disagreement of our results could be explained by the amount of radiation doses of participants which was too low to cause a statistically significant difference in examined parameters between two years. Due to the bimonthly recorded doses by film badge dosimeters, MPs were exposed to the well below accepted standards doses.

Besides, some investigators have reported that, there is temporary hematopoietic recovery in healthy individuals after ionizing radiation exposures (Lushbaugh, Eisele, Burr Jr, Hubner, & Wachholz, 1990; Müller & Streffer, 1991). As shown by El-Shanshoury et al. (El-Shanshoury et al., 2016) and some others studying on animal models, the blood cells recover within several days and weeks after low dose radiation exposure. Moreover as shown by Seed et al, hematopoietic repair was increased in canines under variable levels of chronic radiation (Seed, 1996). They have reported that following the radiation exposures, blood cells count began to declining

and then began to rebound. The difference between the mean values of RBCs, WBCs and platelet count after recovery course in present of such chronic low dose radiation will not be significant in animal models.

Pluripotent stem cells are master cells, which produce any cell or tissue that the body needs to repair itself, but these cells are quiet radiosensitive. Ionizing radiation exposure can damage stem cells of the hematopoietic system. Some investigators reported that tolerance to hematopoietic failure at low dose-rates is mainly unknown but probably linked to stem cell responses to radiation exposure (Fliedner et al., 2012). This might be explained by persistence of radio-resistant subpopulations within hematopoietic stem cells and progenitor cell compartments (Sidorov, Kimura, Yashin, & Aviv, 2009).

The conflicts between our results and other studies are may be due to differences in radiation dose, and follow up duration of target group (MPs). The present study suggests that more studies with grater sample size and various follow up duration are required to study the long term effects of X-ray radiation on medical professionals' HPs.

5. Conclusion

It appears that, working with C-Arm x-ray machine, with regard of radiation protection regulations, the hematological parameter cannot be a reliable survey as biomarker of long term exposure to very low doses of radiation exposure for MPs.

Acknowledgments

The Author would like to thank the medical professionals who agreed to participate in this research.

Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- Andreassi, M. G., Cioppa, A., Botto, N., Joksic, G., Manfredi, S., Federici, C., ... Picano, E. (2005). Somatic DNA damage in interventional cardiologists: A case-control study. *The FASEB Journal*, *19*(8), 998-999. http://dx.doi.org/10.1096/fj.04-3287fje
- Billings, P. C., Romero-Weaver, A. L., & Kennedy, A. R. (2014). Effect of Gender on the Radiation Sensitivity of Murine Blood Cells. *Gravitational and space research: Publication of the American Society for Gravitational and Space Research*, 2(1), 25-31.
- Caciari, T., Capozzella, A., Tomei, F., Nieto, H., Gioffrè, P., Valentini, V., ... Chighine, A. (2011). Professional exposure to ionizing radiations in health workers and white blood cells. *Annali di igiene: Medicina preventiva e di comunita*, 24(6), 465-474.
- Clerinx, P., Buls, N., Bosmans, H., & De Mey, J. (2008). Double-dosimetry algorithm for workers in interventional radiology. *Radiation protection dosimetry*, 129(1-3), 321-327. http://dx.doi.org/10.1093/rpd/ncn148
- Elgazzar, A. H., & Kazem, N. (2015). Biological effects of ionizing radiation the pathophysiologic basis of nuclear medicine (pp. 715-726). Springer.
- El-Shanshoury, H., El-Shanshoury, G., & Abaza, A. (2016). Evaluation of low dose ionizing radiation effect on some blood components in animal model. *Journal of Radiation Research and Applied Sciences*. http://dx.doi.org/10.1016/j.jrras.2016.01.001
- Fliedner, T. M., Graessle, D. H., Meineke, V., & Feinendegen, L. E. (2012). Hemopoietic response to low dose-rates of ionizing radiation shows stem cell tolerance and adaptation. *Dose-Response*, 10(4), dose-response. 12-014. Feinendegen. http://dx.doi.org/10.2203/dose-response.12-014. Feinendegen
- Fritz, T. (2002). The influence of dose, dose rate and radiation quality on the effect of protracted whole body irradiation of beagles. *Brit J Radiol suppl*, 26, 103-111.
- Hrycek, A., Czernecka-Micińska, A., Kłuciński, P., & Badowski, R. (2002). Peripheral blood lymphocytes and selected serum interleukins in workers operating X-ray equipment. *Toxicology letters, 132*(2), 101-107. http://dx.doi.org/10.1016/S0378-4274(02)00030-9
- Klein, L. W., Miller, D. L., Balter, S., Laskey, W., Haines, D., Norbash, A., ... Laboratory, J. I.-S. T. F. O. O. H. I. T. I. (2010). Occupational health hazards in the interventional laboratory: Time for a safer environment. *Journal of Radiology Nursing*, 29(3), 75-82. http://dx.doi.org/10.1016/j.jradnu.2010.06.003
- Lushbaugh, C., Eisele, G., Burr Jr, W., Hubner, K., & Wachholz, B. (1990). Current status of biological indicators to detect and quantify previous exposures to radiation. Biological Indicators Working Group.

- Health physics, 60, 103-109.
- Meo, S. A. (2004). Hematological findings in male x-ray technicians. Saudi medical journal, 25(7), 852-856.
- Muirhead, C., O'Hagan, J., Haylock, R., Phillipson, M., Willcock, T., Berridge, G., & Zhang, W. (2009). Mortality and cancer incidence following occupational radiation exposure: Third analysis of the National Registry for Radiation Workers. *British journal of cancer*, 100(1), 206-212. http://dx.doi.org/10.1038/sj.bjc.6604825
- Müller, W.-U., & Streffer, C. (1991). Biological indicators for radiation damage. *International journal of radiation biology*, *59*(4), 863-873. http://dx.doi.org/10.1080/09553009114550771
- Ossetrova, N. I., Sandgren, D. J., Gallego, S., & Blakely, W. F. (2010). Combined approach of hematological biomarkers and plasma protein SAA for improvement of radiation dose assessment triage in biodosimetry applications. *Health physics*, *98*(2), 204-208. http://dx.doi.org/10.1097/HP.0b013e3181abaabf
- Radiation, U. N. S. C. O. T. E. O. A. (2012). Biological mechanisms of radiation actions at low doses: A white paper to guide the Scientific Committee's future programme of work.
- Roguin, A., Goldstein, J., & Bar, O. (2012). Brain tumours among interventional cardiologists: A cause for alarm. Report of four new cases from two cities and a review of the literature. *Euro Intervention*, 7(9), 1081-1086. http://dx.doi.org/10.4244/EIJV7I9A172
- Rozgaj, R., Kašuba, V., Šentija, K., & Prlić, I. (1999). Radiation-induced chromosomal aberrations and haematological alterations in hospital workers. *Occupational medicine*, 49(6), 353-360. http://dx.doi.org/10.1093/occmed/49.6.353
- Sanzari, J. K., Cengel, K. A., Wan, X. S., Rusek, A., & Kennedy, A. R. (2014). Acute hematological effects in mice exposed to the expected doses, dose-rates, and energies of solar particle event-like proton radiation. *Life sciences in space research*, 2, 86-91. http://dx.doi.org/10.1016/j.lssr.2014.01.003
- Sanzari, J. K., Wan, X. S., Krigsfeld, G. S., Wroe, A. J., Gridley, D. S., & Kennedy, A. R. (2013). The effects of gamma and proton radiation exposure on hematopoietic cell counts in the ferret model. *Gravitational and space research: Publication of the American Society for Gravitational and Space Research, 1*(1), 79.
- Seed, T. M. (1996). Hematopoietic tissue repair under chronic low daily dose irradiation. *Advances in Space Research*, 18(1), 65-70. http://dx.doi.org/10.1016/0273-1177(95)00792-D
- Semple, J. W., Italiano, J. E., & Freedman, J. (2011). Platelets and the immune continuum. *Nature Reviews Immunology*, 11(4), 264-274. http://dx.doi.org/10.1038/nri2956
- Shortt, C., Al-Hashimi, H., Malone, L., & Lee, M. (2007). Staff radiation doses to the lower extremities in interventional radiology. *Cardiovascular and interventional radiology*, 30(6), 1206-1209. http://dx.doi.org/10.1007/s00270-007-9071-0
- Sidorov, I., Kimura, M., Yashin, A., & Aviv, A. (2009). Leukocyte telomere dynamics and human hematopoietic stem cell kinetics during somatic growth. *Experimental hematology*, *37*(4), 514-524. http://dx.doi.org/10.1016/j.exphem.2008.11.009
- Siiskonen, T., Tapiovaara, M., Kosunen, A., Lehtinen, M., & Vartiainen, E. (2014). Monte Carlo simulations of occupational radiation doses in interventional radiology. *The British journal of radiology*.
- Singer, G. (2005). Occupational radiation exposure to the surgeon. *Journal of the American Academy of Orthopaedic Surgeons*, 13(1), 69-76. http://dx.doi.org/10.5435/00124635-200501000-00009
- Smirnova, O. A. (2010). *Environmental radiation effects on mammals: A dynamical modeling approach*. Springer Science & Business Media. http://dx.doi.org/10.1007/978-1-4419-7213-2
- Venneri, L., Rossi, F., Botto, N., Andreassi, M. G., Salcone, N., Emad, A., ... Picano, E. (2009). Cancer risk from professional exposure in staff working in cardiac catheterization laboratory: Insights from the National Research Council's Biological Effects of Ionizing Radiation VII Report. *American heart journal*, 157(1), 118-124. http://dx.doi.org/10.1016/j.ahj.2008.08.009
- Von Boetticher, H., Lachmund, J., & Hoffmann, W. (2008). Effective dose estimation in diagnostic radiology with two dosimeters: Impact of the 2007 recommendations of the ICRP. *Health physics*, 95(3), 337-340. http://dx.doi.org/10.1097/01.HP.0000318877.79131.08
- Vorobiev, A. I. (1997). Acute radiation disease and biological dosimetry in 1993. *Stem Cells*, 15(S1), 269-274. http://dx.doi.org/10.1002/stem.5530150736

- Whitby, M., & Martin, C. (2014). Radiation doses to the legs of radiologists performing interventional procedures: Are they a cause for concern? *The British journal of radiology*.
- Yang, F. E., Vaida, F., Ignacio, L., Houghton, A., Nautiyal, J., Halpern, H., ... Vijayakumar, S. (1995). Analysis of weekly complete blood counts in patients receiving standard fractionated partial body radiation therapy. *International Journal of Radiation Oncology Biology Physics*, 33(3), 607-617. http://dx.doi.org/10.1016/0360-3016(95)00255-W
- Yousuf, R., Mobin, M. H., & Leong, C. F. (2015). Gamma irradiation and red cell haemolysis: A study at the Universiti Kebangsaan Malaysia Medical Centre. *The Malaysian journal of pathology*, *37*(2), 91-94.

Copyrights

Copyright for this article is retained by the author(s), with first publication rights granted to the journal.

This is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).